REMARKS

Claims 1-25 are currently pending: claims 20-22 stand rejected and claims 1-19 and 23-25 have been withdrawn for being directed to non-elected subject matter. With this amendment, claims 1-19 and 23-25 have been cancelled. Applicants expressly reserve the right to pursue the canceled subject matter in this application or in future applications claiming benefit and priority herefrom. With this amendment, claim 20 has been amended and claims 26-32 have been added. Accordingly, upon entry of this amendment, claims 20-22 and 26-32 constitute the pending claims of the application.

Examiner Interview Summary: Applicants appreciate the time and attention of Examiners Gembeh and Marschel during the telephonic interview of February 14, 2008 with applicants' representatives. During the interview, the status of the rejected claims was discussed in light of the outstanding enablement and obviousness-type double patenting rejections. Specifically, applicants' representatives explained that claims reciting identical method of treatment language based on the same specification and same working examples were found by two different U.S. patent examiners to be enabled in both the parent application, now U.S. Patent No. 6,653,326 (Exhibit A) and a divisional application filed on the same day as the pending application, now U.S. Patent No. 7,148,239 (Exhibit B). The only difference between the claims of those issued patents and the claims of the current divisional application is that a different subgenus of compounds (those of Formula I") is recited in the pending claims. The Office indicated that Applicants should submit a written reply explaining this situation and briefly summarizing the allowed subject matter of both issued patents. Applicants have included below a summary of the allowed claims of U.S. Patent Nos. 6,653,326 and 7,148,239 that pertain to the subject matter claimed in the present application. Applicants address substantively the enablement rejections in more detail following that summary.

U.S. Patent No. 6,653,326: U.S. Patent No. 6,653,326 ("the '326 patent") claims methods for increasing activity or expression of a molecular chaperone via the administration of compounds of formula (I) (see, e.g., claim 1 and dependent claims). The '326 patent also claims methods for the treatment or prevention of a disease connected with the function of the chaperone system or

associated with the injury of the membrane of a cell or cell organellum via the administration of compounds of formula (I) (see, e.g., claim 12 and dependent claims). Additionally, the '326 patent claims compounds and compositions of the invention as depicted by formula (I) (see, e.g., claims 23 and 30, and dependent claims).

U.S. Patent No. 7,148,239: U.S. Patent No. 7,148,239 ("the '239 patent") claims methods for increasing activity or expression of a molecular chaperone via the administration of compounds of formula (II) for treatment of physiological stress accompanying a variety of diseases or conditions (see, e.g., claims 1 and 11, and dependent claims). The '239 patent also claims methods for the treatment or prevention of a diseases connected with the function of the chaperone system or associated with the injury of the membrane of a cell or cell organellum via the administration of compounds of formula (II) (see, e.g., claim 17 and dependent claims). Additionally, the '239 patent claims compounds and compositions of the invention as depicted by formula (II) (see, e.g., claims 32 and 34, and dependent claims).

Amendments to the Specification: The specification has been amended to correct inadvertent typographical errors in the title and in the naming of a compound. In particular, in the results depicted in Table 2 on page 125 of the specification as originally filed, the compound 5,6-dihydro-5-(1-piperidinyl)-methyl-(3-pyridyl)-4*H*-1,2,4-oxadiziane is incorrectly named. Evidence for the correct name may be found, for example, on p. 71, line 7 under the heading **Example 64**, in Table 3 on p. 128, line 7, and in Table 4 on p. 130, line 28. The present amendment corrects this inadvertent typographical error in Table 2 of the specification by clarifying that the compound in Table 2 and that of Example 64 are referring to the same chemical composition. Moreover, the skilled artisan reading the instant specification would recognize that the compound named "5,6-dihydro-5-(1-piperidinyl)-methyl-(3-pyridyl)-4*H*-1,2,4-oxadiziane" refers to the same chemical structure as the compound correctly named in Example 64 as "5,6-dihydro-5-(1-piperidinyl)-methyl-**3-**(3-pyridyl)-4*H*-1,2,4-oxadiziane", the only difference (highlighted) being an additional 3- that would be understood based on the structure as a whole. Accordingly, no new matter has been added to the specification as originally filed by this amendment.

Claim Amendments: Claim 20 has been amended to more clearly and distinctly point out the claimed subject matter of the present invention. New claims 26-32 have been added to more particularly point out the present invention. Support for these new claims may be found, for example, on p. 13, lines 17-27 and p. 28, lines 7-30 of the specification as originally filed.

The present amendments add no new matter.

Applicants respectfully request reconsideration in view of the foregoing amendments and following remarks. Issues raised by the Examiner will be addressed below in the order that they appear in the Office Action.

Restriction Requirement – Status of Claims: The Office has asked for re-affirmation of the election of claims 20-22 during a 8/31/07 telephone conversation with applicants' representative, Erika Takeuchi. The Examiner requested that telephonic election due to having mistakenly included claims 23-24 in Group III of the original Restriction Requirement mailed on 8/22/06. Applicants hereby reaffirm the election of Group III (claims 20-22) for initial substantive examination. However, applicants respectfully request that the species election for A be pyridine rather than pyrimidine.

Enablement Rejections Based on 35 U.S.C. 112: Claims 20-22 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. The Office alleges that the claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Office contends that the showing of the activity of the compounds, such as those contained in the Examples on pp. 112-134 of the instant application, do not enable one to practice the instant methods of the pending claims. Applicants respectfully traverse this rejection for at least the reasons detailed below.

First, as discussed above, claim 12 of U.S. Patent 6,653,326 ("the '326 patent") (which issued from U.S. Application 08/860,582 ("the parent application") from which the present application claims priority as a divisional application); and claim 17 of U.S. Patent 7,148,239 ("the

'239 patent") (which is another divisional application also claiming priority to the parent application) each recite language identical to the language of pending claim 20 but for referring to a different compound subgenus. Thus, two different U.S. patent examiners have, at the very least, accepted the nexus between the disclosure and working examples of the instant specification and enablement of the claimed therapeutic methods using compounds of the invention. Turning to the presently claimed subgenus, those of Formula I", the compound produced in Example 64 (p. 71, paragraph 220) (heretofore referred to by its colloquial name "iroxanadine") falls into the Formula I" subgenus of the pending claims and also corresponds to the presently elected species. Iroxanadine was subjected to the same heat stress experiments in the same working examples of the instant specification (see, e.g., Example 19 at pp. 124-133 of the specification) as were the compounds supporting enablement of the claims of the parent and sister applications that issued as the '326 and the '239 patents, respectively.

In addition to the examples disclosed in the application as originally filed, applicants submit herewith Exhibits C-E as post-filing date evidence that the pending method claims are enabled.

Exhibit C: U.S. Patent 6,143,741 ("the '741 Patent"), provides additional experimental data for therapeutic benefits of administering the compound of Example 64 (referred to in the '741 Patent as Compound No. 13; see col. 5, lines 15-16). The '741 Patent includes data relating to vasorelaxing effects of Compound 13 (see Table 1 at col. 8, lines 1-30 relating to endothelial function and vasorelaxing effects of Compound 13 during chemically-induced vasodilation in thoracic aorta of spontaneously hypertensive ("SH") rats, concluding that "tested compounds improved this decreasing vasodilation significantly, which shows the improvement of the endothelial function.") In addition, the '741 Patent includes data from a wounding migration assay on HUVEC cells relevant to repair of damaged vascular monolayers (see col. 11, lines 1-53 and lines 18-22 for Compound 13). Moreover, the '741 Patent also provides *in vivo* data on the effects of oral pre-treatment with compounds, including Compound 13, on reducing the size of infarctions and the extent of myocardial necrosis following induction of myocardial ischaemia in an accepted SH rat model. See, e.g., col. 9, line 26 to column 11, line 55 of the '714 Patent, especially col. 10,

lines 30-55 for Compound 13. Notably, in this *in vivo* study, SH rats treated with compounds ***one month prior to the induced ischaemia*** showed significant improvements in survival rate, reduced infarct size and extent of myocardial necrosis compared to control pre-treated rats. See, e.g., col. 10, lines 53-67. That pre-treating animals with Compound 13 resulted in significant preventative effects in an accepted *in vivo* animal model of myocardial ischaemia supports the prevention element of the currently pending claims.

Exhibit D: U.S. Patent 6,384,029 ("the '029 Patent") provides additional *in vivo* evidence that an optically active isomer of the compound of Example 64 disclosed in the present application ((-)-5,6-dihydro-5-(1-piperidinyl)-methyl-(3-pyridyl)-4*H*-1,2,4-oxadiziane) is effective as a treatment for conditions associated with physiological stress from a coronarial disease, as encompassed by currently pending claim 20. As in Exhibit C described above, here too the results described at col. 3, line 55 -- col. 4, line 30 provide support for methods of prevention as recited in the currently pending claims, because the effective compound was administered 6 hours *before* the physiological stress was induced in the white rabbit.

Exhibit E: U.S. Patent Publication 2006/0058294 provides further experimental data for a group of compounds that fall within the genus of pending claim 20. The oxadiazines of Examples 6-11 are shown in paragraphs 90-91 on pp. 3-4 to improve the functioning of the endothelium following a physiological stress (relating to endothelial function and vasorelaxing effects of compounds during chemically-induced vasodilation in thoracic aorta of spotanteously hypertensive ("SH") rats as described above for Exhibit C). Further evidence of the therapeutic effectiveness of these compounds is provided in the endothelial cell wounding migration assay set forth in paragraphs 86-88 on p. 3. The oxadiazines referred to in Examples 6-11 are all encompassed by the (Formula I") genus of pending claim 20.

In light of the combined weight of the evidence presented in Exhibits C-E and the granted patents in Exhibits A-B, which are part of the same family as the present application, applicants respectfully request reconsideration and withdrawal of the lack of enablement rejections of claims 20-22. The weight of the evidence shows that pending claims 20-32 are fully enabled.

Rejections Based on Obviousness-Type Double Patenting: Claims 20-22 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-34 of U.S. Patent No. 7,148,239 ("the '239 patent). Specifically, the Office contends that both sets of claims refer to treating a disease connected with the function of the chaperone system and that the claimed compounds are obvious variations of the compounds of the method of the '239 patent. Applicants respectfully traverse.

The claims of the '239 patent recite a method of treating a disease connected with the function of the chaperone system by administering the compounds of formula (II) (the '239 patent, claim 17). The compounds of generic formula (II) are acyclic compounds. In contrast, the compounds of pending claims 20-22 recite a method utilizing cyclic compounds of formula (I"). Claims 17-39 of the '239 patent do not teach or suggest that a compound of formula (II) may be a cyclic compound, let alone a cyclic compound of formula (I"). The Office has provided no evidence or even argument to support that compounds or formula (II) would render compounds of formula (I") obvious, except for the conclusory assertion that these compounds are "derivatives." Yet, the acyclic compounds of formula (II) and the cyclic compounds of formula (I") are so structurally distinct that, without more, the Office's unsupported contentions cannot properly sustain the present rejection.

Applicants request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 212.596.9000. Should an extension of time be required, applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to Deposit Account No. 06-1075, under Order No. 004049-0015 from which the undersigned is authorized to draw.

Dated: February 19, 2008

Respectfully submitted,

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